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Understanding the mechanism of the *N*-heterocyclic carbene-catalyzed ring-expansion of 4-formyl-β-lactams to succinimide derivatives

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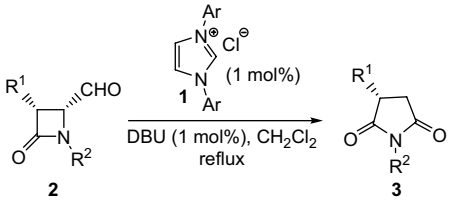
ABSTRACT

The mechanism of the *N*-heterocyclic carbene (NHC)-catalyzed ring-expansion of 4-formyl-β-lactams to succinimides has been studied using DFT methods at the B3LYP/6-31G** level. The first step is the nucleophilic attack of NHC to the aldehyde to yield the zwitterionic intermediate, which by a proton-transfer process affords the Breslow intermediate. The lactam N–C breaking bond in this intermediate yields an enol-amidate, which by a keto–enol type equilibrium becomes the ketone form. The subsequent ring-closure achieved by the nucleophilic attack of the amidate to carbonyl carbon allows the formation of the five-membered ring. Finally, elimination of NHC affords the succinimide. Analysis of the nucleophilicity index correctly explains the behaviors of the NHCs and the Breslow intermediates in the *umpolung* reactivity of aldehydes.

1. Introduction

Succinimides constitute an important compound class due to their wide profile of biological activity.[1] Besides, the succinimide nucleus is a useful building block for the synthesis of natural as well as unnatural products.[2] On the other hand, the use of 2-azetidinones as chiral building blocks in organic synthesis is now well established.[3] Although many efforts have been made in these fields, the preparation of the succinimide ring from the β-lactam nucleus has not been much studied. Recently, Alcaide et al.[4] studied the tetrabutylammonium cyanide-catalyzed ring-expansion of 4-(arylamino)methylazetidin-2-ones to succinimide derivatives.

N-Heterocyclic carbene (NHC) catalysts are being extensively utilized for a variety of transformations by the means of *umpolung*,[5] reversing of the reactivity of aldehydes, providing an unconventional access to some important target molecules.[6,7] Very recently, You[8] and Alcaide[9] have reported that in presence of NHC catalysts, *cis*-4-formyl-β-lactams undergo a ring-expansion to succinimide derivatives (see Scheme 1). Thus, when the *cis*-4-formyl-β-lactam **2** (R^1=Ph, R^2=PMP) was treated with 1 mol % of the imidazolium chloride **1** (Ar=Mes) and DBU, it was smoothly converted to the succinimide **3** in 7 h at reflux in 99% yield.[8a]



Scheme 1.

A plausible catalytic cycle was proposed as illustrated in Scheme 2.[8,9] The NHC **4** would be formed in situ by deprotonation of imidazolium chloride **1** in the presence of DBU, at its most acidic position. The resulting imidazol-2-ylidene, **4**, the actual catalyst, reacts with 4-formyl-β-lactam **2** to give the enoldiamine **5**, which undergoes the ring-opening of 4-formyl-β-lactam releasing the nucleophilic amidate **6**. The nucleophilic amidate **7**, the carbonyl form of **6**, experiments an intramolecular cyclization to give succinimide derivative **8**, which releases the NHC catalyst **4** to yield the succinimide **3**.

The key step of this catalyst cycle is the formation of the enoldiamine **5**, which permits the cleavage of the N1–C4 lactam ring through a *umpolung* reactivity of the aldehyde carbon atom. The N1–C4 cleavage on the 4-formyl-β-lactam **2** will generate a very energetic zwitterionic intermediate **ZW1** in which the C4 positive charge is located closer to the carbonyl carbon atom of the formyl group (see Scheme 3). This unfavorable arrangement prevents the corresponding ring-cleavage on the 4-formyl-β-lactam **2**. However,

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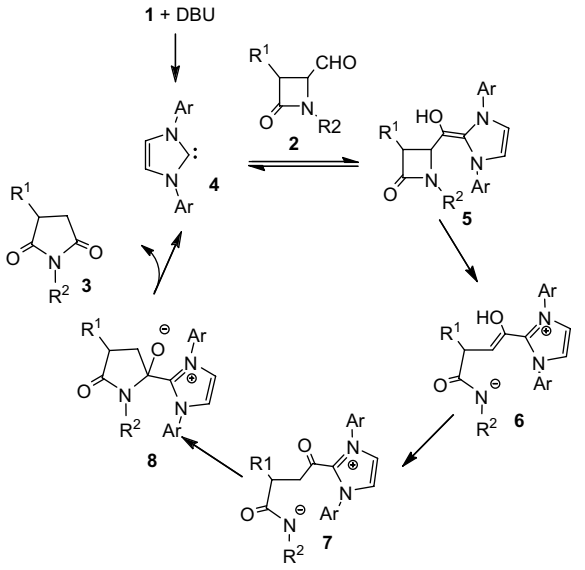
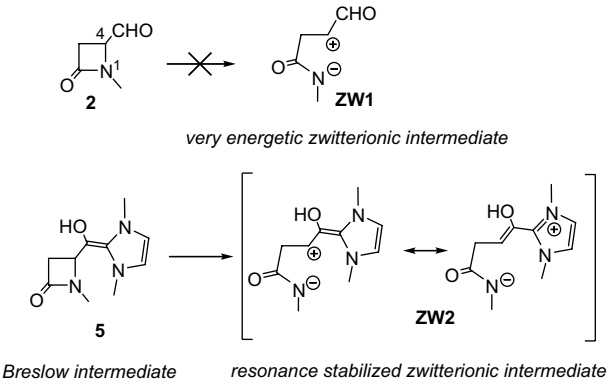


Scheme 2.

the presence of the 2-methyleneimidazole group on **5** favors the corresponding N1–C4 cleavage by a favorable charge delocalization on the C4 carbocationic center, which is being generate along the heterolytic N1–C4 breaking bond.



Scheme 3.

The enoldiamines as **5**, know as Breslow intermediates,[10] are proposed as the key intermediates on the NHC *umpolung* reactivity of aldehydes, because the electron-deficient carbonyl carbon becomes as an electron-rich center to occupy the β-position of the enoldiamine (see Chart 1).

In 1958 Breslow[10] studied the mechanism of the thiazolium catalyzed benzoin condensation. It stated that the key intermediate was compound **12**, which acts as nucleophile like the α-hydroxyl carbanionic intermediate on the cyanide-catalyzed reaction of benzaldehyde to benzoin.[11] These intermediates are highly appreciated d^1-synthons in the *umpolung* reactivity of the aldehydes. In 1964, Lemal et al.[12] proposed that the true mechanism of the benzoin condensation involves the dimerization of the thiazolin-2-ylidene **10** to **15**, and the subsequent addition to benzaldehyde to form, after a proton-transfer process on the adduct **16**, the carbanion **17**. The subsequent C–C breaking bond in **17** will afford the Breslow intermediate **12**. Experimental evidences reported by Lopez-Calahorra et al.[13] indicated that the bis(thiazolin-2-ylidene) **15** acts as catalyst in the benzoin condensation. However, further experimental studies reported by Breslow and Schmuck[14] indicated that the reaction is first order in thiazolium ion thus excluding the participation of anions as **17**.

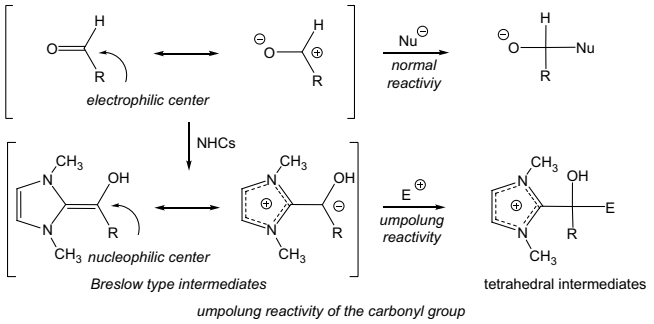
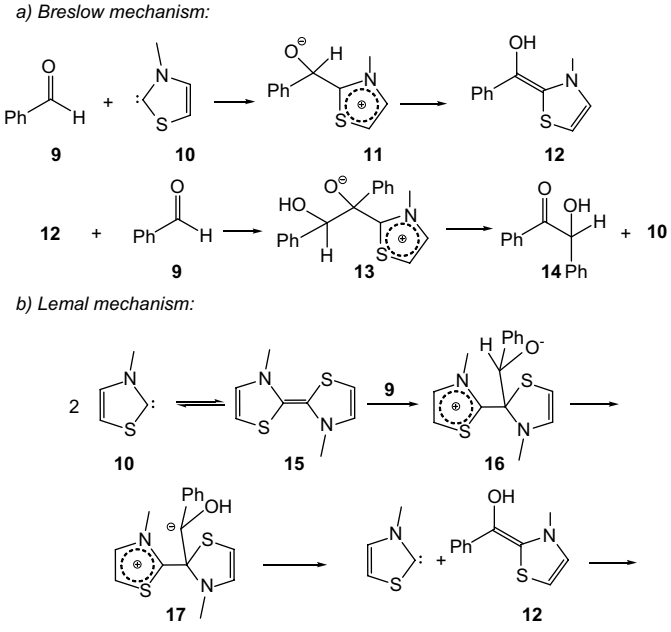


Chart 1.

The NHC catalyzed benzoin condensation has been theoretically studied firstly by Bofill et al.[15] at the AM1 semiempirical level and more recently by Goldfuss and Schumacher[16] using density functional theory (DFT) methods at the B3LYP/6-31G* level. Formation of the Breslow intermediate **12**, which is involved in most of the NHC *umpolung* catalyzed reactions of aldehydes, comprises two steps (see Scheme 4). The first one is the nucleophilic attack of the thiazol-2-yliden carbene **10** to benzaldehyde **9** to yield the alkoxy intermediate **11**, which by a proton-transfer process yields in the second step the Breslow intermediate **12**. Although formation of the intermediates **11** and **12** were slightly exothermic, −1.3 and −5.4 kcal/mol, respectively, the activation energy associated with the proton-transfer process was very high, 38.1 kcal/mol. This unfavorable activation energy was closer to that obtained by Bofill at the AM1 level, 33.2 kcal/mol.[15] The Lemal mechanism was also studied by Bofill et al.[15] at the AM1 semiempirical level. They found that the formation of the alkoxide **16** is endothermic in 18.8 kcal/mol, being the barrier for the proton-transfer process of 64.6 kcal/mol.



Scheme 4.

Our interest in the organocatalysis[17] has prompted us to carry out a series of theoretical investigations about the mechanisms of the NHC catalyzed reactions of aldehydes. In this first study, we would investigate NHC catalyzed ring-expansion of 4-formyl-β-lactams to succinimide derivatives using DFT methods at the well-established B3LYP/6-31G** level. For this propose the